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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,310	12/17/2004	Hidehito Kotani	262507US0PCT	6711

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/517,310	KOTANI ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,29-34,39-43,47 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,29-34,39-43,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 28, 2007 has been entered.

Claims 24, 29-34, 39-43 and 47-48 are currently pending. Claims 24, 29-34, 39-43 are currently amended. Claims 47-48 are newly presented. Claims 39-43 were indicated as withdrawn from further consideration pursuant to 37 CFR 1.142(b) in the Office Action of May 8, 2007, however the examiner has decided rejoin these claims. Therefore claims 24, 29-34, 39-43 and 47-48 have been addressed herein.

Withdrawn Objections

2. The objection made in section 3 of the Office Action of May 8, 2007 is withdrawn in view of amendments made to the claim 24 and the cancellation of claims 25-27.

Withdrawn Rejections

3. The rejections made under 35 USC 112 2nd paragraph in section 6 of the Office Action of May 8, 2007 are withdrawn in view of amendments and/or cancellation of the claims.

The rejections made under 35 USC 102(b) in section 7 of the Office Action of May 8, 2007 are withdrawn in view of the Applicants perfection of the priority claim.

The rejections made under 35 USC 103(a) in sections 8-12 of the Office Action of May 8, 2007 are withdrawn in view of the Applicants perfection of the priority claim.

Claim Rejections - 35 USC § 112 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 29-34, 39-43, and 47-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24, 29-34, 39-43, and 47-48 are indefinite over the recitation of the phrase "the presence of the genomic polynucleotide polymorphism of the ABCG2 gene in which C421A polymorphism occurs at nucleotide position 421 of SEQ ID NO: 1". This phrase is confusing because it leads one to believe that SEQ ID NO: 1 is the genomic sequence of the ABCG2 gene, however SEQ ID NO: 1 appears to only be the coding sequence.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 29-34, 39-43, and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining if a human cell carries a gene which encodes an ABCG2 transporter with decreased capacity to excrete compound B comprising: collecting a biological sample from said human cell and testing the biological sample from said human cell for the presence the polymorphism in the ABCG2 gene in which C421A polymorphism occurs at nucleotide position 421 of SEQ ID NO: 1, wherein the presence of said polymorphism is indicative of a decreased capacity of said ABCG2 transporter for excreting Compound B, wherein the decreased capacity is compared to an ABCG2 transporter that is homozygous (C/C) at position 421 of SEQ ID NO: 1, does not reasonably provide enablement for a method for predicting if a human cells has a decreased capacity to excrete compound B comprising: collecting a biological sample from a human cell, testing the biological sample from said human cell for the presence of the genomic polynucleotide polymorphism of the ABCG2 gene in which C421A polymorphism occurs at nucleotide position 421 of SEQ ID NO: 1, wherein the presence of said genomic polynucleotide polymorphism is indicative of a decreased capacity by said cell to excrete compound B.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

The invention is drawn to a method for predicting if a human cell has a decreased capacity to excrete compound B. The method comprises: collecting a biological sample from a human cell, testing the biological sample from said human cell for the presence of the genomic polynucleotide polymorphism of the ABCG2 gene in which C421A polymorphism occurs at nucleotide position 421 of SEQ ID NO: 1, wherein the presence of said genomic polynucleotide polymorphism is indicative of a decreased capacity by said cell to excrete compound B. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)). The nature of the invention requires the knowledge of a reliable association between the C421A polymorphism of SEQ ID NO: 1 and the ability of a cell to excrete compound B.

Scope of the Claims:

The claims are extremely broad over the recitation of the phrase "decreased capacity" because the standard used to determine whether the capacity is "decreased" is unknown. Further the claims are drawn broadly to detecting C421A polymorphism that occurs at position 421 of SEQ ID NO: 1, wherein the presence of the polymorphism is indicative of a decreased capacity by said cell to excrete compound B. This is problematic because it is not disclosed if both polymorphic alleles (AA) or just one polymorphic allele (CA) is needed to be indicative of a decreased capacity by said cell to excrete compound B. Further it is unknown if there are any other cell transporters that are able to excrete compound B in human cells or other cells. Additionally claims 40 and 41 are extremely broad because they encompass the detection of any allele at position 34 or 376 of SEQ ID NO: 1 in homozygous or heterozygous form. Further it is unclear if these additional polymorphisms have an affect on the cells capacity to excrete compound B. Also Claim 42 is extremely broad because it encompasses the detection of a nucleic acid encoding an amino acid with any substitution at position 12 of SEQ ID NO: 2. Claim 43 encompasses the detection of a nculeic acid encoding an amino acid with any substitution that causes termination at position 126 of SEQ ID NO: 2.

Teachings in the Specification and Examples:

The specification teaches on page 3 that SEQ ID NO 1 represents the ABCG2 gene. It is noted that SEQ ID NO 1 actually only represents the coding regions of the ABCG2 gene and not the entire gene. The specification (page 35) further teaches 2 mutations in the ABCG2 gene (G34A and C421A) that result in amino acid substitutions

in the ABCG2 protein that have a high possibility to affect the function of the ABCG2 polypeptide. Additionally the specification teaches that one mutation (C376T) codes for a stop codon and does not even produce a functional protein. The specification (page 3) also teaches a chemical structure. The specification states that this structure belongs in the class of indolocarbazole compounds and that the protein encoded by SEQ ID NO 1 confers a selective resistance to indolocarbazole compounds. One specific indolocarbazole compound that is disclosed is called "Compound B".

Example 1 in the specification describes the process used by the Applicants for identifying SNPs in the human ABCG2 gene. The results of the identified SNPS in the 30 human cancer cell lines and in the 149 human clinical samples are shown in Table 3. This table shows that the frequency of the G34C mutation was 16.7% in 30 cell lines and 19.5% in 149 human clinical samples. This table shows that the frequency of the C376T mutation was 3.3% in 30 cell lines and 0% in 149 human clinical samples. This table shows that the frequency of the C421A mutation was 20% in 30 cell lines and 16.1% in 149 human clinical samples. Here it is noted that there is no information in the specification on whether the cells and human samples were homozygous or heterozygous for these mutations.

Example 2 in the specification describes how cell lines were prepared that expressed mutated ABCG2. Here two mutations, G34A and C421A were prepared and introduced into porcine kidney cells as an endeavor to analyze their functions. In Example 3, the transfectant cells, which were selected in Example 2, were evaluated on their resistance to Compound B. The results are shown in Table 4. From these results it

was suggested that, the cells with the G34A and C421A mutations have a decreased capability to excrete Compound B.

In the instant case the specification only teaches that the C421A polymorphism in the ABCG2 gene is associated with decreased capacity of a porcine kidney cell to excrete compound B, yet the claims are drawn to human cells. Further it is noted that the specification does not teach if the C421A polymorphism is present in homozygous or heterozygous form, therefore it is unclear if cells which are heterozygous (CA) will also have decreased capability to excrete compound B or it the cells must be homozygous (AA) to have this property. Additionally the specification does not teach which, if any, other cellular transporters are capable of excreting "Compound B". Therefore its unclear if the ABCG2 transporter is mutated whether **the cell** will actually have decreased capacity to excrete Compound B or if just **the ABCG2 transporter** will have decreased capacity to excrete Compound B. Further it is noted that the specification teaches that an "A" at position 34 of SEQ ID NO: 1 and a "T" at position 376 of SEQ ID NO: 1 are both associated with decreased capacity to excrete compound B, however the claims encompass the detection of any allele at these positions and do not specify whether these mutations contribute to the cells capacity to excrete compound B. Also the specification does not teach if these polymorphisms are present in homozygous or heterozygous form, therefore it is unclear if cells which are heterozygous will also have decreased capability to excrete compound B or it the cells must be homozygous to have this property. Finally the specification teaches that an "M" at position 12 of SEQ ID NO: 2 and a stop codon at position 126 of SEQ ID NO: 2 are

both associated with decreased capacity to excrete compound B, however the claims encompass the detection of any amino acid at these positions and do not specify whether these substitutions contribute to the cells capacity to excrete compound B.

State of the Art and the Unpredictability of the Art:

The state of the art at the time of Applicant's filing was underdeveloped with regard to the use of the C421A polymorphism of the ABCG2 gene to predict the likelihood that a human cell has a decreased capacity to excrete compound B.

In the instant case it is highly unpredictable if a method that detects just one allele at position 421 of SEQ ID NO: 1 could be used for identifying a human cell having decreased capacity to excrete compound B. The claims state that an "A" at position 421 of SEQ ID NO: 1 is indicative of a decreased capacity of a cell to excrete compound B. However, based on the teachings in the specification, it is unclear if the cell needs to be homozygous at position 421 (AA) or heterozygous at position 421 (CA) in order to have this property. The specification is silent with regard as to how the presence of one or both polymorphic alleles affects the claimed phenotype. Therefore it is unpredictable if the presence of a single "A" allele at position 421 is indicative of a decreased capacity of the cell to excrete compound B. Further based on the lack of teachings in the specification it is unclear if a skilled artisan would have to look at both alleles to determine if a cell has a decreased capacity to excrete compound B.

Additionally it is highly unpredictable as to whether the presence of the polymorphic at position 421 of SEQ ID NO: 1 will actually cause the cell to have a decreased capacity to excrete compound B. The specification does not teach if the

ABCG2 pump is the only pump in human cells that excretes compound B. The pre-filing date of Komatani (page 2827) teaches that the ABCG2 transporter is a member of a large super family of proteins that transport a wide variety of substrates. Komatani further teaches that some members of this family are thought to play an important role in the drug resistance of cancer cells to anticancer agents. Cancer cells expressing such ABC transporters exhibit decreased intracellular concentrations of drug because of active efflux by the transporters, which cause drug resistance. Two other members of this family have been shown to be involved in resistance to multiple anticancer drugs, P-gp and MRPI. Therefore it highly unpredictable whether the presence of the polymorphic at position 421 of SEQ ID NO: 1 will actually cause the cell to have a decreased capacity to excrete compound B because it is unclear if the ABCG2 transporter is not working whether the cell has additional ways of excreting compound B. In the instant case the specification has only shown that if the ABCG2 transporter is mutated, the ABCG2 transporter will have decreased capacity to excrete Compound B, not the entire cell.

Quantity of Experimentation:

The specification teaches that the presence of an "A" allele at position 421 of SEQ ID NO: 1 is indicative of a decreased capacity for a cell to excrete compound B. In the instant case the specification is silent with regard as to whether the cell needs to be homozygous at position 421 (AA) or heterozygous at position 421 (CA) in order to have this property. To answer this question one of skill in the art would have to conduct extensive experimentation. For example, such experimentation may involve sequencing

the ABCG2 gene of individuals, separating the individuals into three groups based on whether they have the CC, CA, or AA allele at position 421 of SEQ ID NO: 1, and then evaluating each group on their resistance to compound B. Such random, trial by error experimentation is considered to be undue. While methods for sequencing genes are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for mutations that may linked to a disease. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification only teaches that if the ABCG2 transporter is

mutated, the ABCG2 transporter will have decreased capacity to excrete Compound B. However the Applicants are claiming that if the ABCG2 transporter is mutated the cell with have a decreased capacity to excrete Compound B. Further the claims are drawn to detecting the presence of a polymorphism in homozygous or heterozygous form wherein the presence of the polymorphism is indicative of decreased capacity of the cell to excrete compound B. However the specification does not teach if the cell needs to have one or both polymorphic alleles to have this property. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response To Arguments

6. In the response filed September 28, 2007, Applicants thanked the examiner for referring to enabled subject matter and amended the claims accordingly. Based on the amendments the Applicants believe that the enablement rejection is moot. However after further consideration of the application the examiner has identified more issues with regard to enablement. These issues have been addressed in the enablement rejection presented above.

Conclusion

7. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER